

Total Synthesis of Salimabromide: A Tetracyclic Polyketide from a Marine Myxobacterium

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S Supporting Information

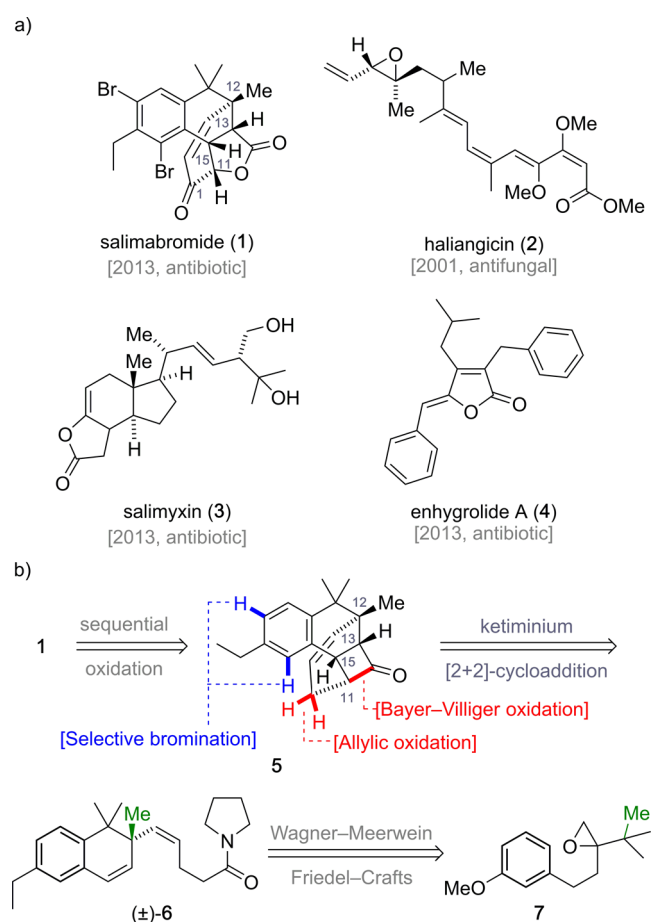
ABSTRACT: Salimabromide is an antibiotic polyketide that was previously isolated from the obligate marine myxobacterium *Enhygromyxa salina*, and its densely functionalized and conformationally rigid tetracyclic framework is unprecedented in nature. Herein we report the first chemical synthesis of the target structure by employing a series of well-orchestrated, robust transformations, highlighted by an acid-promoted, powerful Wagner–Meerwein rearrangement/Friedel–Crafts cyclization sequence to forge the two adjacent quaternary carbon centers embedded in the tetrahydronaphthalene. A high-yielding ketiminium mediated [2+2]-cycloaddition was also utilized for the simultaneous construction of the remaining three stereocenters.

Myxobacteria of terrestrial origin produce an abundance of structurally complex secondary metabolites with notable biological activities. Prominent examples include epothilone, coralopyronin and soraphen.¹ Marine myxobacteria, on the other hand, have eluded their cultivation and isolation on many occasions and constitute a largely unexplored treasure trove of bioactive molecules.² Haliangicin (**2**), which was reported in seminal work by Fudou in 2001,³ represents the first natural product isolated from a strictly marine myxobacterium (Scheme 1a). Following this early report, only a handful of new marine myxobacterium molecules have appeared in the literature,² and in 2013, König disclosed the isolation of salimabromide (**1**) in minute quantities (0.5 mg from 64 L of culture) from the obligate marine bacterium *Enhygromyxa salina*.⁴ Although a broad biological screening campaign was impossible at this stage, **1** was shown to possess inhibitory activity against *Arthrobacter crystallopoietes* (16 $\mu\text{g mL}^{-1}$).

From a structural point of view, salimabromide (**1**) contains an unprecedented tetracyclic ring-architecture that contains four consecutive stereocenters, one of which is quaternary. Additionally, the brominated tetrahydronaphthalene core is bridged at C12 and C15 to form a highly substituted and synthetically challenging seven-membered carbocycle.⁵ The conformational flexibility of this subunit is further reduced by fusion to a five-membered lactone.

The structure for **1** was exclusively deduced from extensive NMR measurements. Though this only confirmed the

Scheme 1. (a) Structural Diversity Produced by Marine Myxobacteria and (b) Key Retrosynthetic Bond Disconnections for Salimabromide (**1**)



connectivity, the absolute stereochemistry was determined by comparison of calculated and measured CD spectra.

Despite considerable progress of the Menche group,⁵ no total synthesis of salimabromide (**1**) has been accomplished to date. In light of these considerations, we set out to develop a practical synthetic route to enable rapid access to **1** and fully

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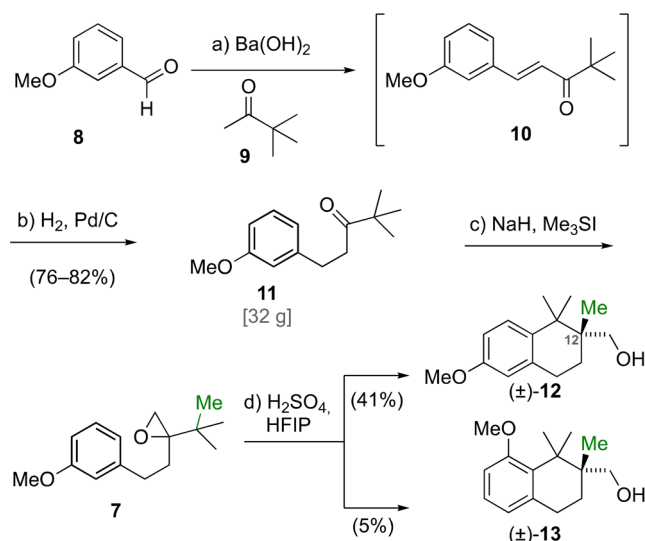
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synthetic derivatives thereof. Herein we describe a streamlined synthesis of **1** employing a series of robust chemical transformations. The successful realization of this route allowed us to produce 1.9 g of a highly advanced intermediate in a single batch from which salimabromide (**1**) was prepared in only three steps.

Our retrosynthetic bond disconnections were guided by our desire to rapidly generate molecular complexity and to install the individual stereocenters via a minimum number of synthetic operations (Scheme 1b). We planned to first install the pivotal C12 quaternary carbon center and utilize this handle for the subsequent one-step construction of the stereotriad along C11, C13 and C15. For this purpose and in analogy to the logic of two-phase terpene (bio)synthesis,⁶ salimabromide (**1**) was first reduced to tetracycle **5**. This intermediate was designed to eliminate steric hindrance and cross-reactivity of the bromine substituents en route to the tetracyclic carbon framework of **1**. Compound **5** contains the retron for a powerful ketiminium mediated [2+2]-cycloaddition⁷ to produce the simplified dihydronaphthalene **6**. Further C–C bond disconnections involving truncation of the side chain and a retro-Friedel–Crafts cyclization/Wagner–Meerwein⁸ rearrangement sequence provided epoxide **7**.

We commenced our synthesis with the Claisen–Schmidt condensation of commercially available 3-methoxybenzaldehyde **8** with pinacolone **9** (Scheme 2). Though slow reactions

Scheme 2. Synthesis of the Tetrahydronaphthalene Framework via Consecutive Wagner–Meerwein Rearrangement and Friedel–Crafts Cyclization



^aReagents and conditions: (a) $[\text{Ba}(\text{OH})_2 \cdot \text{H}_2\text{O}, \text{C-200}]$, pinacolone **9**, EtOH, 78 °C; (b) Pd/C, H_2 , EtOAc, 23 °C, 76–82% over two steps; (c) NaH, DMSO, 70 °C, then Me_3SI , 0 to 23 °C; (d) H_2SO_4 , HFIP, 23 °C, 41% for **12**, 5% for **13** over two steps.

(48 h) and moderate yields (48%) were observed for standard bases such as sodium or potassium hydroxide, the use of activated barium hydroxide $[\text{Ba}(\text{OH})_2 \cdot \text{H}_2\text{O}, \text{C-200}]$ ⁹ led to rapid consumption of the reactants and clean conversion to the condensation product **10**. On large scale, **10** was best obtained by simple filtration of the reaction mixture using a pad of Celite and evaporation of excess ethanol and pinacolone **9**. The following heterogeneous hydrogenation (1 atm H_2 , Pd/C, EtOAc) was conducted on large-scale and reproducibly

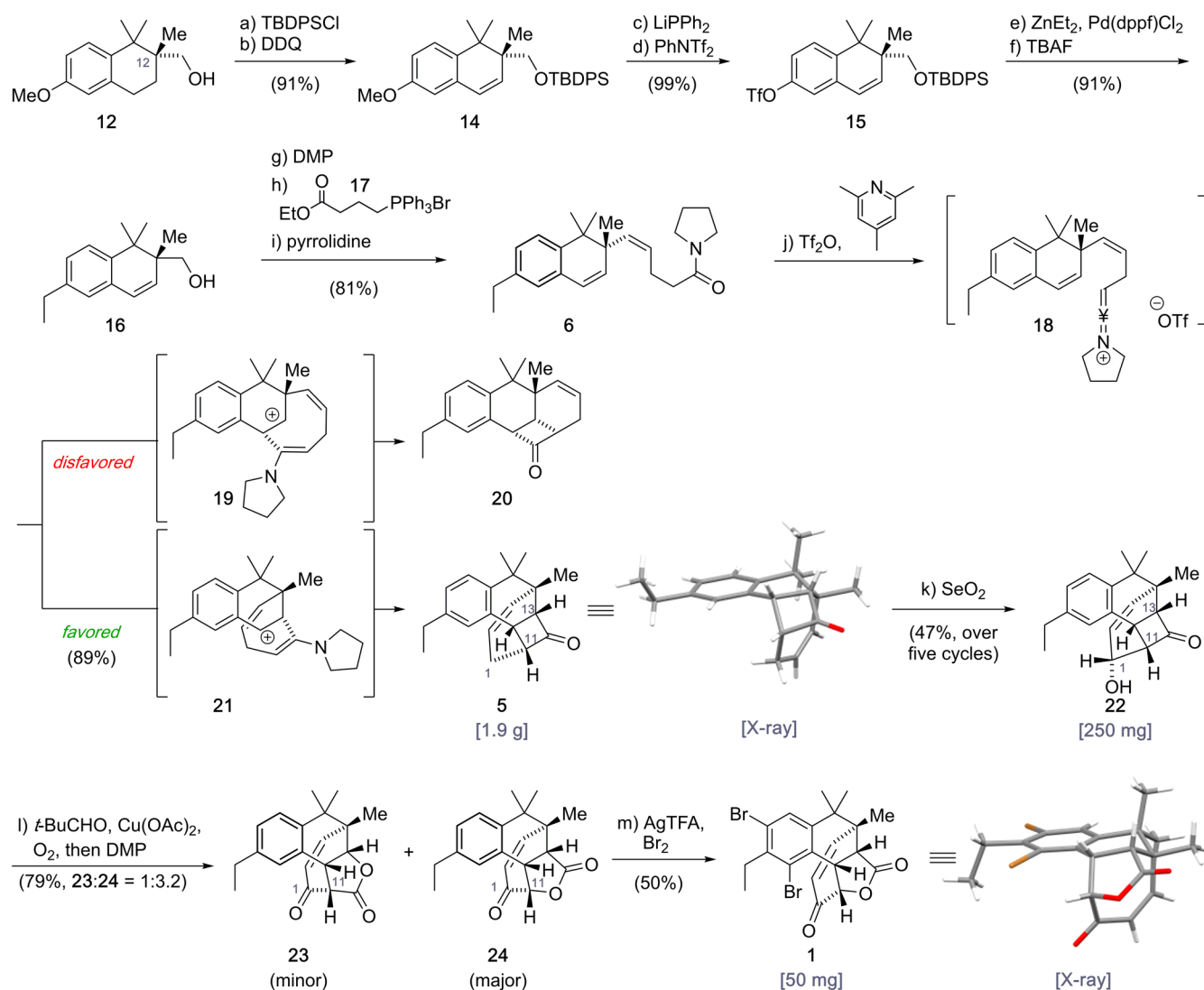
provided **11** in good yield (76–83% over two steps, 32 g). Exposure of **11** to standard Corey–Chaykovsky conditions (NaDMSO , Me_3SI , 0 to 23 °C)¹⁰ effected clean conversion to epoxide **7**. With **7** in hand, we investigated the crucial rearrangement-cyclization sequence. We found that exposure of **7** to hexanes/sulfuric acid or dichloromethane/titanium(IV) chloride was low-yielding for **12** (~30%) and afforded substantial amounts of the undesired *ortho*-product **13** (~10%). Further screening revealed 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 0.1 M), a strong hydrogen-bond donor and weak nucleophile,¹¹ as the solvent of choice and concentrated sulfuric acid as the optimal catalyst (10 mol %). Under these conditions, the *para*-product **12** was formed with very good regioselectivity (**12**:**13** = 8:1). The remainder of the mass balance corresponds to a complex mixture of byproducts.¹² Similar results were obtained when the reaction was conducted in a hexameric resorcinarene capsule.¹³ In agreement with related Lewis-acid catalyzed semipinacol and Wagner–Meerwein rearrangements,¹⁴ a high level of stereoselectivity should be possible for the initial rearrangement step. Evidence was obtained when a solution of enantiomerically enriched **7** (82% ee) in dichloromethane was exposed to titanium(IV) chloride at –78 °C. Under these conditions, an enantiomeric excess of 70% was obtained for **12** (see Supporting Information for details). This result provides an opportunity to access **1** in an asymmetric fashion.

Having successfully installed the crucial C12 quaternary stereocenter in only four steps, we turned our attention to the remaining functionalization of **12** (Scheme 3). To begin, the primary alcohol was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether, and styrene **14** was then formed via exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2 equiv).¹⁵ The use of substoichiometric amounts of DDQ (30 mol %) in combination with manganese(IV) oxide (6 equiv) or alternative oxidation agents such as chloranil, Pd/C or electrochemical methods (4 V, chloranil, Pt/Pt, 0.1 M LiClO_4 , MeCN) were ineffective.

The TBDPS group was crucial for the stability of the silyl ether under the reaction conditions, and the presence of the electron-donating methoxy substituent was beneficial for the oxidation.¹⁶

For the installation of the missing ethyl substituent, we initially investigated the direct coupling of **14** using nickel (e.g., $\text{Ni}(\text{acac})_2$, dcyte, EtMgBr , MgI_2 , PhMe, 100 °C; $\text{Ni}(\text{cod})_2$, dcyte, EtMgI , MgI_2 , PhMe, 100 °C).¹⁷ Because our substrate proved to be remarkably unreactive under these conditions, we decided to replace the methoxy substituent with a more reactive triflate. For the removal of the methyl ether, freshly prepared lithium diphenylphosphide (Ph_2PH , *n*-BuLi) was found to be optimal.¹⁸ The free phenol was then converted to the triflate upon exposure to the Hendrickson–McMurray reagent (PhNTf_2)¹⁹ to afford **15** in quantitative yield. Standard Negishi cross-coupling ($\text{Pd}(\text{dppf})\text{Cl}_2$, ZnEt_2 , dioxane, 70 °C)²⁰ enabled clean installation of the missing ethyl substituent (92%), and cleavage of the silyl ether (TBAF, THF, 23 °C) gave alcohol **16** (99%). The remaining carbon-chain was introduced in a three-step sequence beginning with the oxidation of **16** using Dess–Martin periodinane²¹ (96%), followed by a high-yielding, *Z*-selective Wittig olefination and amide formation (pyrrolidine, 100 °C) to provide **6** (85%).

With robust access to the dihydronaphthalene **6**, we proceeded to investigate the key-step of our synthesis: a ketiminium ion mediated [2+2]-cycloaddition⁷ to construct

Scheme 3. Total Synthesis of Salimabromide^a

^aReagents and conditions: (a) TBDPSCI, imidazole, DMAP, DMF, 23 °C; (b) DDQ, dioxane, 93 °C, 91% over two steps; (c) LiPPh₂, THF, 60 °C; (d) PhNTf₂, NEt₃, THF, 23 °C, 99% over two steps; (e) ZnEt₂, Pd(dppf)Cl₂, dioxane, 70 °C, 92%; (f) TBAF, THF, 23 °C, 99%; (g) DMP, K₂CO₃, CH₂Cl₂, 0 to 23 °C, 96%; (h) NaHMDS, 17, THF, -78 to +23 °C, 85%; (i) pyrrolidine, 100 °C, 99%; (j) Tf₂O, 2,4,6-collidine, ClCH₂CH₂Cl, 80 °C, 89%; (k) SeO₂, SiO₂, dioxane, 120 °C, 47% over five cycles; (l) *t*-BuCHO, Cu(OAc)₂, O₂ (1 atm), ClCH₂CH₂Cl, 23 °C, then DMP, NaHCO₃, CH₂Cl₂, 79%, 23:24 = 1:3.2; (m) AgTFA, Br₂, CF₃COOH, 50%.

the seven-membered carbocycle and complete the tetracyclic carbon framework. Under optimized conditions, a solution of amide **6** and *sym*-collidine (1.2 equiv) in dichloroethane was slowly added to a refluxing solution of freshly distilled trifluoromethanesulfonic anhydride (1.2 equiv) in dichloroethane (0.1 M). The cycloaddition produced the tetracycle **5** with almost perfect regio- and diastereoselectivity in excellent yield (89%, 1.9 g). The exact mechanism, concerted (synchronous/asynchronous) or stepwise, has been a matter of debate for many decades.⁷ Depending on the substitution pattern on both the alkene and the ketiminium salt, either of the two pathways might be operational.²² The greater resonance stabilization of the benzylic cation **21** versus **19** was envisioned to govern the regioselectivity favoring formation of **5**.

Having installed the crucial stereocenters, we were poised to tackle the remaining challenges: regioselective oxidation of the carbon-framework and bromination of the arene subunit.

When **5** (500 mg) was treated with selenium dioxide (dioxane, 120 °C, 6 h) in the presence of silicon dioxide (>230 mesh) to prevent agglomeration, the diastereomerically pure allylic alcohol **22** was formed together with unreacted **5**. Extended reaction times were detrimental as overoxidation and decomposition started to prevail. Subjection of recovered **5** (76%) to the reaction conditions enabled us to prepare 250 mg of **22** after five cycles (47%, ~15% for the first cycle).²³ Subsequent Baeyer–Villiger oxidation using standard conditions (*m*-CPBA, NaHCO₃, CH₂Cl₂) gave two regioisomeric lactones, which were directly oxidized (DMP, NaHCO₃, CH₂Cl₂) to afford **23** and **24** in a ratio of 1.4:1 in 84% combined yield. Separation of **23** and **24** was readily accomplished by flash column chromatography. To improve this undesired outcome, further optimization of the oxidant was performed. Interestingly, exposure of **22** to *t*-BuCHO (5 equiv) in the presence of molecular oxygen (1 atm) and copper(II) acetate (1 equiv) gave **24** as the major product

(79%, 23:24 = 1:3.2).²⁴ The directing effect of the free hydroxy group was crucial as the corresponding methyl ether led to lower regioselectivity (1:1.1) only slightly favoring the desired regioisomer (compare 24). It is also noteworthy that replacement of *t*-BuCHO with *m*-CPBA in the Baeyer–Villiger step under otherwise identical conditions was even less efficient and only poor regioselectivity (23:24 = 1.2:1) was obtained. For the introduction of the missing bromine substituents, 24 was exposed to a panel of brominating agents (e.g., Br₂, CHCl₃; NBS, HOAc; BnMe₃NBr₃, ZnBr₂, HOAc). Under these conditions, formation of 1 was only observed in trace amounts if at all. Finally, we found that treating a solution of 24 in trifluoroacetic acid (0.1 M) with silver(I) trifluoroacetate (3 equiv) and elemental bromine (3 equiv) enabled the desired bromination (50%) and thus completed the synthesis of salimabromide (1, 50 mg).²⁵ The analytical data for 1 (¹H NMR, ¹³C NMR, HRMS) fully matched those reported for the natural compound. Additionally, the structure of 1 was unambiguously validated by single-crystal X-ray diffraction analysis.

In summary, we have completed the first total synthesis of salimabromide, a unique tetracyclic polyketide. The highlights of the developed route are (1) a powerful Wagner–Meerwein rearrangement/Friedel–Crafts cyclization sequence to forge the tetrahydronaphthalene skeleton and (2) a high-yielding ketiminium mediated (2+2)-cycloaddition to set the remaining three stereocenters. The overall sequence benefits from a series of practical transformations that can be also conducted on large scale. The robustness of the developed synthesis is evident from the fact that more than 1.9 g of a highly advanced intermediate were prepared in a single batch.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06228.

Experimental details and spectroscopic data (PDF)
X-ray crystallographic data for 1, 5, 23 and 24 (CIF)

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Notes

The authors declare no competing financial interest.

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